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EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/526,741	ABURATANI ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/1/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20060601*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The response filed on 5/1/06 to the restriction requirement of 3/27/06 has been received. Applicant has elected Group II, claims 8-16 for examination. Because applicant did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse MPEP 818.03(a).

2. Claims 8-16 are currently pending and under examination.

3. The change of the title of the application to, Antibody Against Secreted N-terminal Peptide of GPC3 Present in Blood or C-terminal Peptide of GPC3, has been entered.

4. It is noted that examiner has established a priority date for the instant application, 10/526,741, of September 4, 2003 because the priority of the instantly claimed invention is based on the Japanese patent, number PCT/JP02/08999, which has not been translated and examiner is unable to determine the information in the document. If applicant disagrees with any rejection set forth in this action based on examiner's establishment of a priority date, September 4, 2003, for the instantly claimed application serial number 10/526,741, applicant is invited to submit a proper translation of the priority document and to point to, page and line where support can be found establishing an earlier priority date.

Specification Objections

5. The disclosure is objected to because of the following informalities: residue is misspelled on p .7, line 24.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 9-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to antibody to residues 359-580 and 375-580. However, there is no SEQ ID NO: given to provide a point of reference as to what the amino acids in fact are claimed.

8. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 12 is indefinite because it recites the phrase a "chimera antibody". The exact meaning of the word chimera is not known. The term chimera is generic to a class of antibodies, which are products of genetic shuffling of antibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to CDR grafted antibodies. Even if the specification discusses an embodiment included in an indefinite term, such as chimera, this discussion is not limiting unless the specification specifically defines the term "chimera" and states something like, for the purposes of this invention, the term chimera means, indicates, whatever. Since the term chimera

is indefinite, in the absence of this definition, the recitation of the term "chimera" in the claims is still indefinite.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies against the C-terminal peptide of GPC 3, does not reasonably provide enablement for said antibodies wherein said C-terminal peptide of GPC 3 is a peptide comprising amino acid residues 350-580/375-580 of GPC3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are drawn to an antibody against a C-terminal peptide of GPC3 wherein said C-terminal peptide of GPC 3comprises amino acid residues 359-580/375-580 of GPC 3. This means that the claimed antibody binds to a C-terminal peptide of GPC 3, as defined by the

claims, that is, it binds to a peptide that comprises amino acid residues 359-580/375-580 of GPC3, but is not required to bind residues that are in fact found on any GPC3. This means antibodies that the claims define, a C-terminal peptide of GPC3, as any polypeptide that comprises amino acid residue 350-580/375-580 of GPC3 and reads on antibodies that bind to the undefined portions of the claimed polypeptides.

In the instant application, the specification teaches that the GPC3 C-terminal peptide of GPC3 is about 30 kDa (p.8, 4th para.) based on the cleavage site of GPC3 that is described as being amino acid residue 358, residue 374, or a region in the vicinity thereof (pp. 7-8, para. 5 and 1). Furthermore, the C-terminal peptide is preferably a peptide of an amino acid sequence of from Ser 359 to His 580 or a peptide of an amino acid sequence of from Val 375 to His 580 (p.8, para 4). The instant application does not however fully describe the peptide antigens comprising the C-terminal peptide wherein the C-terminal peptide of GPC 3 is a peptide comprising amino acids 359-580/375-580 of GPC 3.

One cannot extrapolate the teaching of the specification to the scope of the claims because there is insufficient guidance and direction as to how to make and use antibodies against GPC C-terminal peptides wherein the antibodies bind to sequences outside of the disclosed fragments. "Comprising" and "having" are open term-language and include amino acid sequences outside of the fragments recited in the claims and contemplated in the specification. Although the example of an antibody to the C-terminal peptide of GPC 3 is given in Fig. 4 and Example 2, applicant has not enabled one skilled in the art to make and/or use antibodies wherein the amino acid sequence outside of the fragments is unknown other than C-terminal

peptide wherein the C-terminal peptide of GPC 3 is a peptide of amino acids 359-580/375-580 of GPC 3.

One cannot extrapolate the teaching of the specification to the scope of the claims because the courts have found that definition of an antibody by its binding affinity to an unknown is not enabling. In particular, the court teaches as follows: "Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites En zo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen". *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 1/20/2004).

To reiterate, applicant is claiming antibodies against unknown sequences and since an antibody is defined by its antigen binding capability, claims drawn to unknown antibodies that bind to unknown antigens are not enabled. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predictably make or use the broadly claimed antibodies with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

12. Claims 9 and 10 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 9 and 10 are drawn to antibodies against polypeptides comprising the C-terminal peptide wherein the C-terminal peptide of GPC 3 is a peptide comprising amino acids 359-580/375-580 of GPC 3. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics.... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a peptide antigen product itself logically cannot adequately describe an antibody to that antigen product.

Thus, the instant specification may provide an adequate written description of the peptide antigens comprising the C-terminal peptide wherein the C-terminal peptide of GPC 3 is a peptide comprising amino acids 359-580/375-580 of GPC 3, per Lilly by structurally describing a representative number of peptide antigens or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe peptide antigens in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any protein comprising the C-terminal peptide wherein the C-terminal peptide of GPC 3 is a peptide comprising amino acids 359-580/375-580 of GPC 3, nor does the specification provide any partial structure of such peptide, nor any physical or chemical characteristics of the said GPC 3 C-terminal peptide nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses two C-terminal polypeptides of GPC 3, this does not provide a description of genus of polypeptide s to which the claimed antibody is against.

The specification also fails to describe the peptide antigen to which the antibodies are against by the test set out in Lilly. The specification describes only two C-terminal GPC 3 polypeptides. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the claimed written description of the peptide antigens comprising the C-terminal peptide wherein the C-terminal peptide of GPC 3 is a peptide comprising amino acids 359-580/375-580 of GPC 3 to which the claimed antibodies are against, that is required to practice the claimed invention. Since the specification fails to adequately describe the antigen to which the claimed antibody is against, it also fails to adequately describe the antibody because an antibody cannot be described by its binding affinity to as unknown antigen.

13. Claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

According to In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1998), the claimed invention should be enabled so that any person skilled in the art can make and use the invention without undue experimentation. See also *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent

coupled with information known in the art without undue experimentation.") See also MPEP § 2164.01(a) and § 2164.04. Factors to consider in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). The factors include the nature of the invention, the breadth of the claims, the state of the prior art, the relative skilled of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to cytotoxic antibodies and cell disrupting agents comprising antibodies/anti-cancer agents comprising said antibody. This means that the claims are drawn to cancer treatment antibodies, and by inference, the treatment of cancer as contemplated in the specification.

It is noted that other than teaching that the invention relates to the antibody where the C-terminal peptide of GPC3 is a peptide comprising amino acid residues 359-580/375-580 of GPC3, neither the claims nor the specification define the C-terminal peptide in a limiting manner, thus it is assumed for examination purposes that the C-terminal peptide includes all of the residues of GPC 3 other than the most N-terminal residue.

As drawn specifically to GPC3, the specification teaches that the antibodies to GPC3 could be used for diagnosis and treatment of cancer (p. 6, para. 3) and that antibodies to the C-terminal of GPC3, in particular are useful for treatment of cancer (p. 68, 2nd para.). The specification specifically notes that the expression of GPC3, as measured at the mRNA level by GeneChip analysis, is at significantly higher levels in poorly differentiated hepatoma lesions versus normal

controls (p. 42, para. 2, Figs. 1 and 3). The specification teaches that monoclonal antibodies were obtained that detected the C-terminal peptide of GPC3 by Western blotting (p.50, 1st para.), the C-terminal peptide consisting of amino acid residues 359-580/375-580 of GPC3 (SEQ ID NO: 4), but could not detect the secreted form of GPC3 which contains the N-terminal portion of said protein (Table 1). The antibodies, ch.M3C11 and ch.M1E07, to the C-terminal peptide of amino acid residues 359-580/375-580 were shown to effectively mediate antibody dependent cellular cytotoxicity (p. 64, 2nd para.) and compliment dependent cytotoxic activity (p.67, 2nd para.) in *in vitro* assays using cell lines. The specification speculates that if said antibodies are used for treating hepatoma, the antibodies can efficiently reach hepatoma cells without being trapped by the secreted form of GPC3, the N-terminal peptide, present in blood. Thus, such antibodies are useful as agents for disrupting cancer cells and as anticancer agents (p. 68, 2nd para.).

One cannot extrapolate the teaching of the specification to the scope of the claims because the claims are drawn to antibodies that can be used as anti-cancer agents and, thus, in fact read on treatment of hepatoma as specifically contemplated in the specification.

It is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable. Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). As drawn to the unpredictability of the cancer therapy arts, the refractory nature of cancer to drugs is well known

in the art. Jain (*Sci. Am.*, 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (*Crit. Rev. in Oncology/Hematology*, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2).

It is clear that, based on the state of the art, no one skilled in the art would accept the assertion that the invention would function as contemplated by the specification or inferred by the claims based only upon the showing that mRNA for GPC3 is differentially expressed in human hepatoma. Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the stare of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in

the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skilled in the art to predict that the invention would function as contemplated or inferred with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

14. If applicant were able to overcome the rejection set forth above, claims 13-16 would still be rejected under 35 USC 112, first paragraph, because the specification, while enabling for a cytotoxic, anti-cancer agent comprising an antibody to SEQ ID NO: 4 amino acids 359-580 or 375-580, does not reasonably provide enablement for a cytotoxic, anti-cancer agent to the C-terminal peptide of GPC3.

It is noted that, for reasons described above, it is assumed for examination purposes that the claims are drawn to C-terminal peptide includes all of the residues of GPC 3 other than the most N-terminal residue. This means the purpose of this rejection is only drawn to the teaching that the antibody must be to the defined C-terminal .

The specification teaches that monoclonal antibodies were obtained that detected the C-terminal peptide of GPC3 by Western blotting (p.50, 1st para.), the C-terminal peptide consisting of amino acid residues 359-580/375-580 of GPC3 (SEQ ID NO: 4), but could not detect the secreted form of GPC3 which contains the N-terminal portion of said protein (Table 1). The antibodies, ch.M3C11 and ch.M1E07, to the C-terminal peptide of amino acid residues 359-580/375-580 were shown to effectively mediate antibody dependent cellular cytotoxicity (p. 64, 2nd para.) and compliment dependent cytotoxic activity (p.67, 2nd para.) in in vitro assays using cell lines. The specification speculates that if said antibodies are used for treating hepatoma, the antibodies can efficiently reach hepatoma cells without being trapped by the secreted form of GPC3, the N-terminal peptide, present in blood. Thus, such antibodies are useful as agents for disrupting cancer cells and as anticancer agents (p. 68, 2nd para.).

It cannot be determined from the specification whether the target antigen, that is GPC3 C-terminal peptide, is presented by the cell in such a way as to permit the antibody to bind to the target in vivo.

As to whether the GPC3 C-terminal peptide is presented by hepatoma cells, in vivo, in such a way as to permit the antibody to bind to the target GPC3 C-terminal peptide, it is noted that GPC3 protein exists on the cell surface and is recognized by antibodies ch.M3C11 and ch.M1E07 which bind to the GPC3 C-terminus from amino acid residues 359-580/375-580 of SEQ ID NO: 4, as exemplified in the specification. However, it cannot be determined from the information in the specification whether it is present in sufficient concentration on a sufficient number of cancer cells to allow for successful therapeutic targeting or whether the protein is modulated, or down-regulated, whether the claimed antibody cross-reacts with antigens with

sequence identity to the claimed peptides. It is absolutely clear that any expression on other cell types, cross-reactivity would substantially interfere with the contemplated and claimed uses for the claimed antibodies and make the contemplated and claimed uses unpredictable. How would one treat a cancer cell if the antibody is sequestered by epitopes shared by proteins other than the target protein on cells other than the cancer cell, how would one treat if GPC3 C-terminal peptide is not present on the cell surface in sufficient concentration on a sufficient number of the cancer cells to permit effective treatment. In particular, White et al. (2001, Ann. Rev. Med., 2001, 52:125-145), teach that, for a successful targeting and immunotherapy, besides specificity of the antibody for the antigen, other prosperities of the antigen should be considered including the following: (1) the antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating; and (2) whether antigens are shed, modulated, or internalized influences the effectiveness of the administered immunotherapy (i.e. the antibody) (p.125, 2nd para.). Additionally, antigen internalization or down regulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p. 126, para. before last). Thus, even if the GPC3 C-terminal peptide is expressed, differentially expressed, presented at the cell surface, it cannot be predicted if the receptor is present on a sufficient number of cancer cells, and in sufficient quantity, to allow for successful diagnostic or therapeutic targeting of cancer cells. In view of the above, one cannot predict whether the GPC3 C-terminal peptide is expressed in sufficient amount on cancer cells such that the claimed monoclonal antibodies would function as contemplated or claimed. Additionally, it cannot be predicted whether the antigen sheds, or is modulated, internalized, or down regulated in primary cancer cells. Thus, it would require undue

experimentation to determine if and under what circumstances the claimed antibodies would be useful as contemplated and claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the stare of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed or contemplated with a reasonable expectation of success. For the above reasons, it appear that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 101

35 U.S.C. §101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

15. Claims 8-11, 13-16 are rejected under 35 USC §101 because the claimed invention is directed to a non-statutory subject matter. The antibody as claimed has the same characteristics as antibodies found naturally.

The claims, as written, do not sufficiently distinguish over antibodies that exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hands of man, an antibody against a C-terminal peptide of GPC 3 is considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of the term "isolated" or "purified," provided no new matter is introduced. See MPEP 2105.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 8, 11, 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Capurro et al. (Amer. Assoc. Can. Res., March, 2002, 43: 219, abstract #1097, IDS).

The claims are drawn to an antibody against a C-terminal peptide of GPC3 (Claim 8), wherein the antibody is a monoclonal antibody (claim 11), a cell disrupting agent comprising the antibody (Claim 14), the cell disrupting agent in Claim 14, wherein the cell is a cancer cell (Claim 15), and anti-cancer agent comprising the antibody (Claim 16).

It is noted that the preamble recitation of a cell disrupting agent or anti-cancer agent (Claims 14-16) is merely suggestive of an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredient, per se, which is the antibody to the C-terminal of GPC3.

It is noted that other than teaching that the invention relates to the antibody where the C-terminal peptide of GPC3 is a peptide comprising amino acid residues 359-580/375-580 of GPC3, neither the claims nor the specification define the C-terminal peptide in a limiting manner, thus it is assumed for examination purposes that the C-terminal peptide includes all of the residues of GPC 3 other than the most N-terminal residue.

Capurro et al. teach a monoclonal antibody to the C-terminus of GPC3.

The product of the prior art comprises the same product as claimed in the instant invention, that is, a monoclonal antibody to the C-terminal peptide of GPC3, thus the claimed product is anticipated because the product will inherently be an antibody against the C-terminal peptide of GPC3 with cell disrupting and anti-cancer activity. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Although the reference does not specifically state that the antibodies were cell disrupting or anti-cancer agents, the claimed product appears to be the same as the prior art product, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior

art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from that taught by the prior art and to establish patentable differences. See In re Best, 562 F2nd 1252, 195 USPQ 430 (CCPA 1977).

17. Claims 8, 13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Huber (PhD Dissertation, Washington University, published December 1998).

The claims are drawn to an antibody against a C-terminal peptide of GPC3 (Claim 8), wherein the antibody is a cytotoxic antibody (Claim 13), a cell disrupting agent comprising the antibody (Claim 14), the cell disrupting agent in Claim 14, wherein the cell is a cancer cell (Claim 15), and anti-cancer agent comprising the antibody (Claim 16).

It is noted that the preamble recitation of a cell disrupting agent or anti-cancer agent (Claims 14-16) is merely suggestive of an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredient, per se, which is the antibody to the C-terminal of GPC3.

It is noted that other than teaching that the invention relates to the antibody where the C-terminal peptide of GPC3 is a peptide comprising amino acid residues 359-580/375-580 of GPC3, neither the claims nor the specification define the C-terminal peptide in a limiting manner, thus it is assumed for examination purposes that the C-terminal peptide includes all of the residues of GPC 3 other than the most N-terminal residue.

Huber teaches anti-GPC3 antibodies (page 152, first line). The anti-GPC3 antibodies taught by Huber are polyclonal antibodies raised against GPC3 in 14-16 week pre-term amniotic

fluid (page 152, line 1+, Figure 27:), which inherently possesses IgG molecules, as evidenced by the Janeway and Travers (pp.8:22-8:23 and Fig. 8:20) -- which teaches that IgG is the only class of immunoglobulin capable of crossing the placenta. The IgG immunoglobulin inherently mediates ADCC response, as evidence by Sanchez-Mejorada *et al.* (*J Leukocyte Biology*, 1998, Vol 63, pages 521-533) who teach that the Fc receptor for IgG (FcγR) binds to the Fc portion and activates ADCC responses by NK cells (page 525 column 1 paragraph 2+; page 525 column 2 paragraph 4; page 526 column 2 Figure 3). Given that it is assumed for examination purposes that the C-terminal peptide includes all of the residues of GPC3, other than the most N-terminal residue, given that the antibodies are polyclonal antibodies, it would be expected that at least a subset of the polyclonal antibodies would bin to the C-terminal peptide of GPC3.

Although Huber does not specifically teach that the cells are cancer cells it would be expected that the antibody would bind to any and all cell types that express the GPC3 antigen. Thus, absent a showing of unobvious differences, the antibody that binds to carcinoma cells taught by Huber appears to be the same as of the instant invention. Since the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on Applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best, 562 F2nd 1252, 195 USPQ 430 (CCPA 1977) and Ex Parte Gray 10 USPQ 2nd 1922 (PTO Bd, Pat. App & Int, 1989).

All the limitations of the claims are met.

18. Claims 8, 11-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Aburatani et al. (U. S. Pat. App. No: 10/481,524, Pub No.: US2004/0236080 A1, June 21, 2002, A1).

The claims are drawn to an antibody against a C-terminal peptide of GPC3 (Claim 8), wherein the antibody is a monoclonal antibody (Claim 11), wherein the antibody is a chimera antibody (Claim 12), wherein the antibody is a cytotoxic antibody (Claim 13), a cell disrupting agent comprising the antibody (Claim 14), the cell disrupting agent in Claim 14, wherein the cell is a cancer cell (Claim 15), and anti-cancer agent comprising the antibody (Claim 16).

It is noted that the preamble recitation of a cell disrupting agent or anti-cancer agent (Claims 14-16) is merely suggestive of an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredient, per se, which is the antibody to the C-terminal of GPC3.

It is noted that other than teaching that the invention relates to the antibody where the C-terminal peptide of GPC3 is a peptide comprising amino acid residues 359-580/375-580 of GPC3, neither the claims nor the specification define the C-terminal peptide in a limiting manner, thus it is assumed for examination purposes that the C-terminal peptide includes all of the residues of GPC 3 other than the most N-terminal residue.

Aburatani et al. teach anti-GPC3 monoclonal and chimeric anti-GPC3 antibodies that mediate antibody-dependent cell mediated cytoxicity against hepatic cancer cells (see claims 1-12). Given that it is assumed for examination purposes that the C-terminal peptide includes all of the residues of GPC3, other than the most N-terminal residue, it would be expected that the anti-GPC3 antibodies would bind to the C-terminal peptide.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131 antedating the applied art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Capurro et al. (Amer. Assoc. Can. Res., March, 2002, 43: 219, abstract #1097, IDS), in view of Queen *et al.* (Proc. Natl. Acad. Sci. 1989, Vol. 86, pages 10029-10033), and in further view of Riechmann et al. (Nature Vol. 332:323-327 1988).

The claims are drawn to an antibody against a C-terminal peptide of GPC3 wherein the antibody is a chimera (Claim 12).

Capurro et al. teaches a monoclonal, antibody against a C-terminal peptide of GPC3 as set forth above. However, Capurro et al. does not teach a chimera antibody.

Queen et al teach a reproducible technique for making humanized antibodies (page 11030, col. 2 Para. 3) and further teaches that for human applications humanized antibodies are more useful because of their reduced immunogenicity (page 10029, col. 2, para. 2).

Riechmann et al teach the "reshaping of human antibodies for therapy" (see Title) in which a "human IgG1 antibody has been reshaped for serotherapy in humans by introducing the six hypervariable regions from the heavy- and light-chain domains of a rat antibody directed against human lymphocytes" (see Abstract). Thus, Riechmann et al fully disclose how one skilled in the art would use recombinant DNA techniques to sequence, clone and humanize a monoclonal antibody, with a reasonable expectation of success. Further, Riechmann et al provide one skilled in the art with the motivation to humanize the antibodies for use as human pharmaceutical. Riechmann et al teach, "the foreign immunoglobulin can elicit an anti-globulin response which may interfere with therapy or cause complex hypersensitivity." (page 323, column 1, first full paragraph). Humanized "chimeric antibodies have at least two advantages

over mouse antibodies. First, the effector functions can be selected or tailored as desired. Second, the use of human rather than mouse isotypes should minimize the anti-globulin responses during therapy by avoiding anti-isotypic antibodies" (see page 323, bridging paragraph, columns 1-2).

As the level of ordinary skill in the immunology art is quite high, it would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to make monoclonal or humanized or chimeric antibodies to the specificities taught by the prior art. One of ordinary skill in the art would have been motivated to make these antibodies in view of the fact that the GPC3 protein is overexpressed in hepatocellular carcinomas (Capurro et al.) and thus are useful in research, for developing diagnostic *in vivo* or screening methods. One of ordinary skill in the art would have been motivated to make humanized or humanized chimeric antibodies with a reasonable expectation of success because Queen *et al.* teach the advantage of using humanized antibodies to reduce immunogenicity. In addition, Riechmann et al have demonstrated the successful genetically engineering and humanization of rat and mouse antibodies, which are also useful, for example, for *in vivo* imaging.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The

filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

20. Claims 8-16 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention, monoclonal and chimeric antibodies against a GPC3 C-terminal peptide and peptides comprising the amino acid residues of 359-580 or 375-580 of GPC3 that have cytotoxic activity, with the intended use as a cell disrupting agent toward cancer cells and with the intended use as anti-cancer agent, as that of claims 8-18 of copending Application No. 11/414,676.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

If applicant disagrees with any rejection set forth in this office action base on examiner's establishment of a priority date (September 4, 2003) for the instantly claimed application serial number 10/526,741, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date. The priority date is based on this date because earlier filed cases are unavailable.

21. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

PJR

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER